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SHORT COMMUNICATION

Morning cortisol secretion in school-age children is related to the sleep pattern of the preceding night

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Summary Sleep disturbance in childhood is common and a risk factor for poor mental health. Evidence indicates that disturbed sleep is associated with altered hypothalamic-pituitary-adrenal axis (HPAA) activity. Knowledge regarding the association between HPAA-activity and objective sleep measures particularly regarding sleep architecture in school-age children is missing. Sleep-electroencephalography was administered to 113 children aged 6—10 years (including 58 children born very preterm and 55 born at term) during one night at the children's homes and sleep duration, sleep continuity, and sleep architecture were assessed. To assess the cortisol awakening response at the following morning, cortisol secretion was measured at awakening, 10, 20, and 30 min later. Regression analyses controlling child age, gender, prematurity status, and the awakening time revealed that morning cortisol secretion was negatively associated with sleep duration and slow wave sleep and positively associated with the relative amount of Stage 2 sleep during the preceding night. In addition, morning cortisol

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secretion linearly increased with age. In conclusion, associations of sleep disturbance with poor mental health may be confounded with altered HPAA-activity.

1. Introduction

Sleep disturbances in children are common with around 20% persistently suffering from poor sleep (Fricke-Oerkermann et al., 2007) and they are an important risk factor for problem behavior and poor mental health (Astill et al., 2012). From studies with adults it is known that disturbed sleep is associated with alterations of hypothalamic-pituitary-adrenal axis (HPAA) activity. This relationship is assumed to be bidirectional (for reviews see Elder et al., 2014, and Steiger, 2002). On the one hand, there is evidence that for instance experimental administration of HPAA hormones (i.e., the corticotropin releasing hormone CRH) as well as Cushing's disease, which involves excessive cortisol levels, both lead to sleep alterations including decreases in slow wave sleep (SWS, also referred to as deep sleep, which is considered to be the most restorative sleep state; Van Cauter et al., 2008). On the other hand, experimental sleep restriction results in increased cortisol levels particularly during the following evening (Elder et al., 2014; Steiger, 2002).

Only a few studies, however, have examined the association between objectively assessed sleep and HPAA-activity in childhood. Three studies examined the relationship of sleep duration and sleep continuity with HPAA-activity in school-age children. One study with 8-year-old children applying actigraphic monitoring of sleep showed that short sleep duration was related to increased morning cortisol secretion, while poor sleep efficiency was associated with higher diurnal cortisol profiles as well as a higher cortisol response to social stress (Räikkönen et al., 2010). Similarly, a second study with 9-year old children showed that short and poor sleep as assessed with actigraphy was related to increased afternoon cortisol levels (El-Sheikh et al., 2008). Recently, a third study showed that short sleep assessed in the sleep laboratory among 5—12-year-old children suffering from insomnia symptoms, was related to increased morning cortisol levels (Fernandez-Mendoza et al., 2014). To our knowledge, however, only one study has examined the relationship between HPAA-activity and sleep architecture in children to date. Hatzinger et al. (2013), studying preschool children, showed that morning cortisol secretion was positively related to light sleep (sleep stages 1 and 2) and rapid-eye-movement (REM) sleep as well as negatively related to SWS.

In sum, there is evidence that in children an increased HPAA-activity is associated with shorter sleep duration and poorer sleep continuity, which may reflect a bidirectional relationship. However, research on the association between HPAA-activity and sleep architecture is scarce and missing altogether for school-age children. To fill this gap, the aim of the present study is to examine the relationship between the cortisol awakening response (CAR) with objectively assessed sleep electroencephalography (EEG) for the first time in school-age children aged 6—10 years. The CAR reflects a rapid increase in cortisol levels immediately following awakening which occurs in the majority of adults and can readily be observed from early childhood onwards (Bäumler et al., 2013). It is considered to be a valid marker of HPAA-activity (Elder et al., 2014), which is related to psychopathology in children (Dietrich et al., 2013). Based on the above mentioned findings in children, we consider the following five hypotheses: morning cortisol secretion is negatively associated with (1) sleep duration and (2) sleep continuity (as represented by more sleep efficiency and less nocturnal awakenings) of the preceding night. Moreover, morning cortisol secretion is positively associated with (3) light sleep (Stage 1 sleep and/or Stage 2 sleep) and (4) REM-sleep, as well as negatively associated with (5) SWS of the preceding night. As HPAA-activity was shown to be associated with child age, gender, and gestational age at birth (e.g., Pesonen et al., 2012; Karemaker et al., 2008) we control for these possible confounders.

2. Methods

2.1. Study population

The study included 113 healthy school-age children (age: $M = 8.3$ years, $SD = 1.3$; range: 6.0—10.9; 38 girls; for descriptive statistics see Table 1). Fifty-eight children were born premature (<32 weeks of gestation; mean birth-weight = 1302 g) and 55 were born at term (mean birth-weight = 3338 g). The preterm born group was recruited from children who were treated at the University Children's Hospital Basel (Switzerland) during the post-natal phase. Although all children attended primary school in Switzerland, eight of the preterm children received additional support at school or visited small group classes, while none of the full-term children received additional support. Parents gave written informed consent for the children to participate in the study and assent was obtained from the child. The study was approved by the Ethics Committee of Basel.

2.2. Procedure

Data for the present study were collected at the children's homes during the regular school week (i.e., the children went to school during both the day before and the day after sleep and cortisol assessment). Trained study personnel administered in-home sleep-EEG.

Table 1 Descriptive statistics for study variables and Pearson's correlations of child characteristics with sleep and cortisol indices.

		Mean/count	(SD/%)	*r*		
				1	2	3
1.	Age, years	8.26	(±1.28)			
2.	Gender, male[a]	75	(66.4%)	−.08		
3.	Prematurity status, born preterm[b]	58	(51.3%)	−.06	−.06	
Sleep variables						
4.	Total sleep time (h)	9.48	(±0.69)	−.48***	.20*	−.01
5.	Sleep efficiency (%)	94.51	(±2.55)	−.33***	.07	−.04
6.	Nocturnal awakenings	17.56	(±7.16)	.03	−.10	.29**
7.	Stage 1 sleep (%)	2.75	(±2.34)	.27**	−.03	.03
8.	Stage 1 sleep (min)	18	(±12)	.24*	−.01	.04
9.	Stage 2 sleep (%)	44.73	(±5.74)	.07	.02	.18†
10.	Stage 2 sleep (min)	256	(±40)	−.19†	.12	.19†
11.	Slow wave sleep (%)	24.55	(±5.28)	−.05	−.05	−.17†
12.	Slow wave sleep (min)	145	(±32)	−.21*	.02	−.17†
13.	REM sleep (%)	25.52	(±4.37)	−.19†	.04	−.05
14.	REM sleep (min)	147	(±27)	−.38***	.13	−.07
15.	REM latency (min)	118	(±44)	.20*	−.08	−.07
16.	Awakening time	06:45	(±00:28)	−.17†	.04	−.11
Cortisol awakening response						
17.	AUCg	2.87	(±0.53)	.27**	.01	−.05
18.	AUCi	0.39	(±0.46)	.05	.05	.00

Note: REM = rapid eye movement, AUCg = area under the curve with respect to the ground, AUCi = area under the curve with respect to the increase.

[a] Coding of gender: 1 = male; 2 = female.

[b] Coding of prematurity status: 0 = born at term; 1 = preterm.

† $p < 0.10$.

* $p < 0.05$.

** $p < 0.010$.

*** $p < 0.001$.

2.3. Variables

2.3.1. Assessment of morning cortisol secretion

The parents of the children were instructed to collect four saliva samples on the following morning, with the first one after awakening and 10, 20, and 30 min later. Parents were also instructed that the children were not allowed to eat or drink and brush their teeth until saliva sampling was completed. Awakening times ranged from 5:20 a.m. to 8:33 a.m. (M = 06:45 a.m., SD = 28 min). The assessment of morning cortisol secretion is available for 102 (90.3%) of the children. For statistical analyses the area-under-the-concentration-time-curve (AUC) of morning cortisol secretion was calculated with the AUCg referring to the area under the curve with respect to the ground and the AUCi referring to area under the curve with respect to the increase (Pruessner et al., 2003). Cortisol values were log-transformed before building these features as distributions of cortisol concentrations were skewed.

Saliva samples were collected using the ''Salivette'' device (Sarstedt, Nümbrecht/Germany) consisting of a small cotton swab on which the children gently chewed for approximately 1 min. Thereafter, the cotton swab was transferred into a small plastic tube, the ''Salivette'' container. Free salivary cortisol concentrations were analyzed using a time-resolved immunoassay with fluorometric detection ''Coat-A-Count'' Cortisol RIA from DPC (Diagnostics Products Corporation; obtained through H. Biermann GmbH, Bad Nauheim, Germany).

2.3.2. Sleep assessment

Sleep was assessed during a single night using the Compumedics Somté PSG device (Melbourne, Australia) to record overnight in-home sleep-EEG. In-home sleep EEG was used to reduce the differences between the child's usual sleep conditions and those of the study to enhance the ecological validity of the sleep assessment. EEG signals C3/A2 and C4/A1 EEG, right and left electrooculogram and bipolar submental electromyogram were obtained. The EEG records were scored by experienced raters according to standard procedures (Rechtschaffen and Kales, 1968). The sleep indices include sleep duration (total sleep time = time in bed minus time spent awake in hours), sleep continuity (sleep efficiency = total sleep time/time in bed × 100; nocturnal awakenings = number of arousals from sleep), and sleep architecture (Stage 1 sleep, Stage 2 sleep, SWS [Stages 3 and 4 sleep], REM sleep, and REM-latency). Sleep-EEG data was available for 102 (90.3%) of the children and in 93 (82.3%) of the children both cortisol and sleep assessment was available.

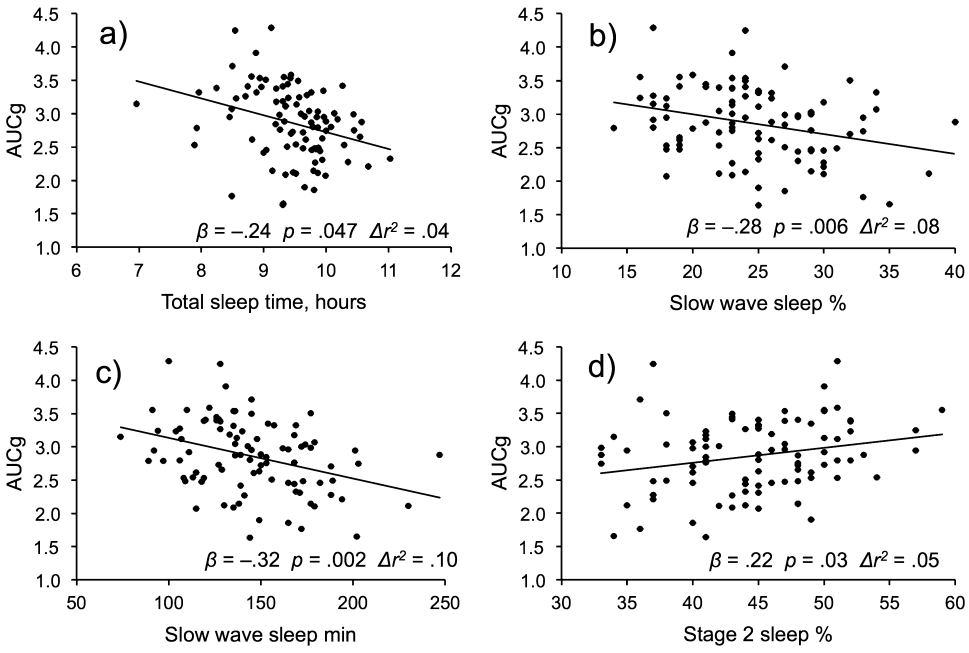

Figure 1 Association of CAR AUCg with (a) total sleep time, (b) slow wave sleep %, (c) slow wave sleep min, and (d) Stage 2 sleep %. Scatterplots show unadjusted values, coefficients are adjusted for child age, gender, prematurity status, and awakening time.

2.4. Statistical analysis

To test our hypotheses, separate regression analyses were conducted with sleep indices as predictors and CAR (AUCg and AUCi) as dependent variables controlling child age, gender, prematurity status, and awakening time using IBM® SPSS® Statistics 20 (IBM Corporation, Armonk NY, USA) for Apple Mac®. The significance level (two tailed) was set at $p < 0.05$.

3. Results

Table 1 shows descriptive statistics as well as Pearson correlations of child characteristics (child age, gender, prematurity status) with sleep variables and morning cortisol secretion. Child age was negatively related to sleep duration, sleep efficiency, SWS min, and REM sleep min, while it was positively associated with the CAR AUCg, Stage 1 sleep and REM sleep latency. Moreover, girls showed longer sleep duration than boys and preterm born children showed more nocturnal awakenings than term born children.

Multiple regression analysis showed that the CAR as represented by the AUCg was negatively associated with sleep duration ($\beta = -.24$, $t = -2.01$, $p = .047$, $\Delta r^2 = .04$, Fig. 1a) and SWS (SWS %: $\beta = -.28$, $t = -2.80$, $p = .006$, $\Delta r^2 = .08$, Fig. 1b; SWS min: $\beta = -.32$, $t = -3.18$, $p = .002$, $\Delta r^2 = .10$, Fig. 1c), controlling for covariates. Moreover, the CAR AUCg was positively associated with Stage 2 sleep (Stage 2 sleep %: $\beta = .22$, $t = 2.15$, $p = .03$, $\Delta r^2 = .05$, Fig. 1d; but not with Stage 2 sleep min: $\beta = .08$, $t = 0.74$, $p = .46$). Sleep efficiency, nocturnal awakenings, Stage 1 sleep, REM sleep, and REM-latency were unrelated with the AUCg (all p-values >.10). Moreover, all sleep indices were unrelated with the CAR AUCi (all p-values >.20). Additionally, results were consistent in terms of effect size and significance when non-parametric correlations were calculated on non-transformed data (i.e., when the AUCg and AUCi were built without prior log-transformation but residualized to control for covariates). As a notable exception, this approach revealed a negative relationship between sleep efficiency and the AUCi ($\rho = -.21$, $p = 0.04$) indicating better sleep efficiency in children with a less strong morning cortisol increase.

4. Discussion

We found that in school-age children morning cortisol secretion, and in particular the AUCg, was negatively associated with sleep duration and SWS of the preceding night and positively associated with Stage 2 sleep. These findings are consistent with studies showing increased HPAA-activity in children with short sleep (El-Sheikh et al., 2008; Fernandez-Mendoza et al., 2014; Räikkönen et al., 2010). Moreover, the findings are consistent with a study showing that among preschoolers, an increased HPAA-activity was associated with more light sleep (i.e., Stage 1 sleep and Stage 2 sleep together) and less SWS (Hatzinger et al., 2013). However, we could not confirm findings of poor sleep continuity (Räikkönen et al., 2010) or increased REM sleep (Hatzinger et al., 2013) in children with increased morning cortisol secretion. Moreover, although there are reports of gender and prematurity related differences regarding HPAA-activity during childhood (Karemaker et al., 2008; Pesonen et al., 2012), we could not confirm such differences regarding the CAR. In contrast to our study, Karemaker et al. (2008) and Pesonen et al. (2012) studied HPAA-reactivity to social stress and/or diurnal cortisol profiles of an entire day, which may account for the different findings. Our finding of an increase of morning cortisol secretion with age is in line with results in young children for whom also an increase of cortisol levels

at awakening from 1 to 7 years of age was reported (Bäumler et al., 2013).

Our study has also limitations. First, the correlational design of the study precludes causal inferences. Second, we assessed sleep-EEG measures and morning cortisol secretion only on a single night and morning. While measurement of the CAR on a single day has limited reliability when it should reflect HPAA-activity on the trait level, this approach is suitable to examine the CAR on a state-level in relation to the sleep pattern of the preceding night, which was the purpose of the present study. However, multiple night EEG and morning cortisol assessment would have allowed disentangling within-person from between-person variation, which may be the aim of future studies. Such future research might possibly elucidate why we found only relations between sleep indices and the CAR AUCg but not with the CAR AUCi, which is difficult to explain based on our current knowledge. Third, we have no objective information regarding participants' compliance with the instructions of saliva sampling which may reduce the reliability of the CAR indices. Finally, our study included more boys than girls and may therefore less well represent the relationship between sleep and HPAA-activity in girls. However, we consider it a strength of the study that sleep was assessed at the children's home, which may have reduced sleep disruption due to unfamiliarity of the environment of a sleep laboratory.

In conclusion, our study shows that in school-aged children, a lower HPAA-activity as represented by a lower CAR AUCg was associated with more restorative sleep including longer sleep duration, less Stage 2 sleep, and more SWS. This pattern of findings points to an interdependence of increased HPAA-activity with less restoring sleep in children. It is therefore conceivable that HPAA-activity plays a major role in the relationship between poor sleep and mental health problems.

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Conflict of interest

The authors declare no conflict of interest.

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References

Astill, R.G., Van der Heijden, K.B., Van IJzendoorn, M.H., Van Someren, E.J., 2012. Sleep, cognition, and behavioral problems in school-age children: a century of research meta-analyzed. Psychol. Bull. 138, 1109—1138.

Bäumler, D., Kirschbaum, C., Kliegel, M., Alexander, N., Stalder, T., 2013. The cortisol awakening response in toddlers and young children. Psychoneuroendocrinology 38, 2485—2492.

Dietrich, A., Ormel, J., Buitelaar, J.K., Verhulst, F.C., Hoekstra, P.J., Hartman, C.A., 2013. Cortisol in the morning and dimensions of anxiety, depression, and aggression in children from a general population and clinic-referred cohort: an integrated analysis. The TRAILS study. Psychoneuroendocrinology 38, 1281—1298.

Elder, G.J., Wetherell, M.A., Barclay, N.L., Ellis, J.G., 2014. The cortisol awakening response — applications and implications for sleep medicine. Sleep Med. Rev. 18, 215—224.

El-Sheikh, M., Buckhalt, J.A., Keller, P.S., Granger, D.A., 2008. Children's objective and subjective sleep disruptions: links with afternoon cortisol levels. Health Psychol. 27, 26.

Fernandez-Mendoza, J., Vgontzas, A.N., Calhoun, S.L., Vgontzas, A., Tsaoussoglou, M., Gaines, J., Bixler, E.O., 2014. Insomnia symptoms, objective sleep duration and hypothalamic-pituitary-adrenal activity in children. Eur. J. Clin. Invest. 44, 493—500.

Fricke-Oerkermann, L., Plück, J., Schredl, M., Heinz, K., Mitschke, A., Wiater, A., Lehmkuhl, G., 2007. Prevalence and course of sleep problems in childhood. Sleep 30, 1371—1377.

Hatzinger, M., Brand, S., Perren, S., Von Wyl, A., Stadelmann, S., von Klitzing, K., Holsboer-Trachsler, E., 2013. In pre-school children, sleep objectively assessed via sleep-EEGs remains stable over 12 months and is related to psychological functioning, but not to cortisol secretion. J. Psychiatr. Res. 47, 1809—1814.

Karemaker, R., Kavelaars, A., ter Wolbeek, M., Tersteeg-Kamperman, M., Baerts, W., Veen, S., Heijnen, C.J., 2008. Neonatal dexamethasone treatment for chronic lung disease of prematurity alters the hypothalamus—pituitary—adrenal axis and immune system activity at school age. Pediatrics 121, e870—e878.

Pesonen, A.K., Kajantie, E., Heinonen, K., Pyhälä, R., Lahti, J., Jones, A., Räikkönen, K., 2012. Sex-specific associations between sleep problems and hypothalamic-pituitary-adrenocortical axis activity in children. Psychoneuroendocrinology 37, 238—248.

Pruessner, J.C., Kirschbaum, C., Meinlschmidt, G., Hellhammer, D.H., 2003. Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. Psychoneuroendocrinology 28, 916—931.

Rechtschaffen, A., Kales, A., 1968. A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects. Washington Public Health Service, US Government Printing Office, Washington, DC.

Räikkönen, K., Matthews, K.A., Pesonen, A.K., Pyhälä, R., Paavonen, E.J., Feldt, K., Kajantie, E., 2010. Poor sleep and altered hypothalamic-pituitary-adrenocortical and sympatho-adrenal-medullary system activity in children. J. Clin. Endocrinol. Metab. 95, 2254—2261.

Steiger, A., 2002. Sleep and the hypothalamo-pituitary-adrenocortical system. Sleep Med. Rev. 6, 125—138.

Van Cauter, E., Spiegel, K., Tasali, E., Leproult, R., 2008. Metabolic consequences of sleep and sleep loss. Sleep Med. 9, S23—S28.